AD_____

Award Number: DAMD17-01-1-0806

TITLE: Bone Geometry as a Predictor of Tissue Fragility and Stress Fracture Risk

PRINCIPAL INVESTIGATOR: Karl J. Jepsen, Ph.D.

CONTRACTING ORGANIZATION: Mount Sinai School of Medicine
New York, New York 10029-6574

REPORT DATE: October 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2004	Annual (10 Sep 2003 - 10 Sep 2004)

4. TITLE AND SUBTITLE
Bone Geometry as a Predictor of Tissue Fragility and Stress Fracture Risk

5. FUNDING NUMBERS
DAMD17-01-1-0806

6. AUTHOR(S)
Karl J. Jepsen, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Mount Sinai School of Medicine
New York, New York 10029-6574

E-Mail: Karl.jepsen@mssm.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Having a narrow tibia relative to body mass has been shown to be a major predictor of stress fracture risk and fragility. The reason for this phenomenon is not understood. Based on studies of genetically distinct inbred mouse strains, we found a reciprocal relationship between bone mass and bone quality, such that slender bones are associated with more damageable bone tissue. *We postulate that a similar reciprocal relationship between bone mass and bone material properties exists in the human skeleton. The intriguing possibility that slender bones, like those we have demonstrated in animal models, may be composed of more damageable material than larger bones has not been considered.* To test this hypothesis, we propose to determine whether whole bone geometry is a predictor of tissue fragility in the tibia from young male donors. Tissue damageability will be assessed from biomechanical testing of compact bone samples and correlated with measures of bone slenderness. Specimens will be subjected to detailed analyses of bone microstructure, composition, and microdamage content. In the second set of experiments, these analyses will be repeated for female donors to test for gender differences in tissue fragility. Further, we will test whether fragility in cortical bone is a predictor of fragility in cancellous bone. Finally, we will conduct ultrasound measurements to identify an ultrasound parameter that is sensitive to the presence of damage and could be used for early diagnosis of stress fractures.

14. SUBJECT TERMS
Stress fracture, Bone Mass, Bone Quality, Biomechanics, Damage, Fatigue, Ultrasound, Non-Invasive measures, Genetic background

15. NUMBER OF PAGES
15

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Having a narrow tibia relative to body mass has been shown to be a major predictor of stress fracture risk and fragility (Giladi et al, 1987; Milgrom et al, 1989; Beck et al, 1996). The reason for this phenomenon is not understood. Based on studies of genetically distinct inbred mouse strains, we found a reciprocal relationship between bone mass and bone quality, such that slender bones are associated with more damageable bone tissue (Jepsen et al, 2001). *We postulate that a similar reciprocal relationship between bone mass and bone material properties exists in the human skeleton. The intriguing possibility that slender bones, like those we have demonstrated in animal models, may be composed of more damageable material than larger bones has not been considered.* To test this hypothesis, we propose to determine whether whole bone geometry is a predictor of tissue fragility in the tibiae from young male donors. Tissue damageability will be assessed from biomechanical testing of compact bone samples and correlated with measures of bone slenderness. Specimens will be subjected to detailed analyses of bone microstructure, composition, and microdamage content. In the second set of experiments, these analyses will be repeated for female donors to test for gender differences in tissue fragility. Further, we will test whether fragility in cortical bone is a predictor of fragility in cancellous bone. Finally, we will conduct ultrasound measurements to identify an ultrasound parameter that is sensitive to the presence of damage and could be used for early, noninvasive diagnosis of stress fractures.

Body

In the third year of this grant, we focused primarily on finishing the tissue-level mechanical tests for the male and female bones. The males bones have been completed and this renewal presents the analysis of this data. Prior renewal communications reported preliminary results for the female tissue mechanical properties. The remaining female mechanical tests will be finished by the end of October, 2004. At this time, we will determine whether females show a similar relationship between bone morphology and bone quality like that observed for the males. In addition, we have begun a series of experiments that examine whether ultrasound has the sensitivity to detect the presence of damage in bone. Most studies have found that ultrasound is insensitive to damage. However, these studies focused primarily on how damage affects the change in the velocity of the ultrasound signal. Velocity is related to the stiffness of the bone and does not address the changes in viscoelastic properties. We have found that damage affects the viscoelastic properties of bone to a greater degree than the stiffness properties and we have focused our attention on the attenuation of the ultrasound signal as this may be more sensitive to the presence of damage. A student for the City University of New York is working on this project and we anticipate results by the end of the Fall semester.

The major outcome of the third year was finishing the testing of male bones and finding that tissue-level mechanical properties do indeed vary with the size of the tibia (Table 1). Tissue modulus decreased with bone size, whereas post-yield strain and total energy increased with bone size. Not all of these correlations were significant indicating that the relationship between bone morphology and tissue level mechanical properties was subtle. This relationship was more dramatic in the mouse femur and particularly dramatic when comparing different bones from different species (Currey, 1984). Nevertheless, post-yield strain and total energy increased significantly with APwidth (Figure 1). These two measures also increased with moment of inertia, but not significantly. The damage parameter decreased with bone size but only when the morphological properties were normalized for body weight and size (Figure 2). These results

indicated that smaller bones are comprised of tissue that is more stiff and less ductile (i.e., more brittle) compared to larger bones.

We also found that bone strength, ductility (as measured by post-yield strain and total energy), and damageability changed significantly with age (Figure 3). Thus, tibiae become weaker, more brittle, and accumulate more damage with age and that these changes begin early in life.

The positive correlation between tissue ductility and bone size may help explain why military recruits and athletes with narrow bones show a higher incidence of stress fractures compared to individuals with wide bones (Giladi et al, 1987; Milgrom et al, 1989; Beck et al, 1996). The increased stress fracture risk for individuals with narrow tibiae was thought to result from increased fatigue damage during intense training because the smaller bone size would lead to higher tissue level stresses (Milgrom et al, 1989; Beck et al, 1996). However, this interpretation was based on the assumption that mechanical properties do not vary among individuals. The current data indicated that tissue-level mechanical properties do, in fact, vary with bone size. Although tissue modulus decreased with tibia size (Table 1, Fig. 1), tissue stresses would be expected to remain higher in narrow tibiae because the ~30% variation in modulus would not be expected to fully compensate for the ~100% variation in section modulus. Importantly, narrower tibia were comprised of tissue that was more brittle and was prone to accumulate more damage compared to tissue from wider tibia (Table 1). Consequently, individuals with narrow tibia may be at higher risk of stress fractures because of higher in vivo tissue stresses (overloading) coupled with a tissue that is more prone to accumulating damage (Figure 4). This would exaggerate the amount of damage in individuals with narrow tibia thereby leading to increased susceptibility to stress fractures. Although testing was conducted in 4-point bending, we expect the results of the monotonic and damage accumulation tests to reflect a generalized variation in tissue properties for these individuals. Thus, variation in tissue-level mechanical properties may play an important role in the pathogenesis of stress fractures.

To determine how the variation in mechanical properties arise from tissue composition and microstructure, we measured the %Ash for each of the test samples and have generated plastic sections for each of the samples. When all of the data was included, we found that %Ash did not vary with any of the morphological traits in a significant manner. Thus, our original hypothesis that small bones would be compensated by increased mineralization was not supported. We have begun a histological analysis to identify microstructural variations including osteon size and density, porosity, % remodeled bone, % osteonal bone, % interstitial bone, and cement line length. This analysis will be completed by December.

In the final year of the grant, we will finish all mechanical and histological testing for the cortical tissue of the male and female bones. These tests should be completed by March 2005. A manuscript for the mechanical properties of the male bones is nearly complete and will be submitted at the end of October, 2004. We anticipate submitting an additional manuscript that details the compositional and microstructural data as explanatory variables. Finally, when the female data is complete, a third manuscript will be submitted detailing the relationship between morphology and material properties for the female skeleton.

TABLE 1. Partial correlation coefficients taking age into consideration. Pearson correlation coefficients are shown with p-values in parentheses. Significant correlations in **bold**. Abbreviations as shown in Table 1.

	Modulus	**Strength**	**Total Energy**	**PY Strain**	**Damageability**
CtAr	-0.24 (0.35)	0.03 (0.90)	0.37 (0.14)	0.40 (0.11)	-0.23 (0.38)
AP Width	-0.09 (0.74)	-0.03 (0.90)	**0.57 (0.02)**	**0.70 (0.01)**	-0.16 (0.55)
ML Width	-0.32 (0.21)	-0.22 (0.39)	0.34 (0.18)	0.41 (0.11)	-0.19 (0.46)
I_{AP}	***-0.45 (0.07)***	-0.10 (0.70)	0.25 (0.34)	0.32 (0.21)	-0.27 (0.30)
I_{ML}	-0.39 (0.12)	-0.18 (0.50)	0.22 (0.39)	0.28 (0.28)	-0.25 (0.33)
J	***-0.43 (0.08)***	-0.13 (0.61)	0.24 (0.35)	0.31 (0.23)	-0.27 (0.30)
AP S	0.36 (0.15)	0.10 (0.69)	0.09 (0.72)	0.03 (0.92)	**0.47 (0.05)**
ML S	0.23 (0.39)	-0.01 (0.96)	0.04 (0.89)	-0.05 (0.84)	***0.42 (0.09)***

FIGURE 1. Post-yield strain (A, C, E) and total energy (B, D, F) correlated with AP-width, ML-width, and the polar moment of inertia of the tibia. Data was age-corrected.

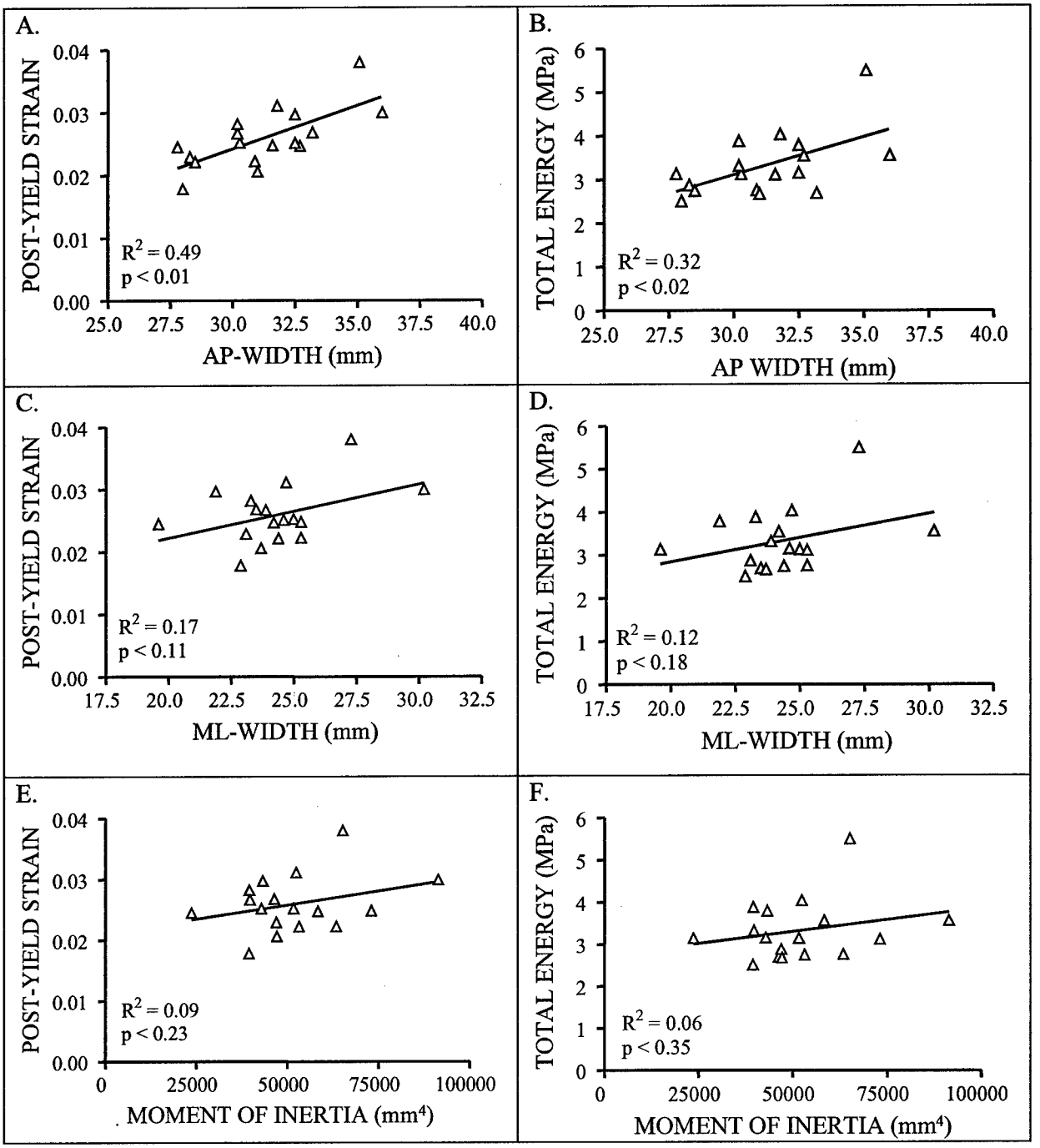


FIGURE 2. Damageability correlated with AP slenderness suggesting that tibiae that were more slender relative to body size and stature were comprised of tissue that accumulated more damage. Data was age-corrected based on a linear regression method.

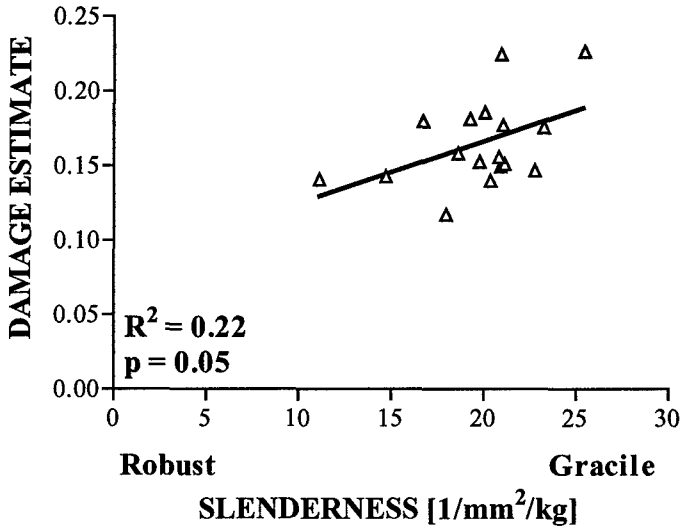


FIGURE 3. Tissue-level mechanical properties change with age.

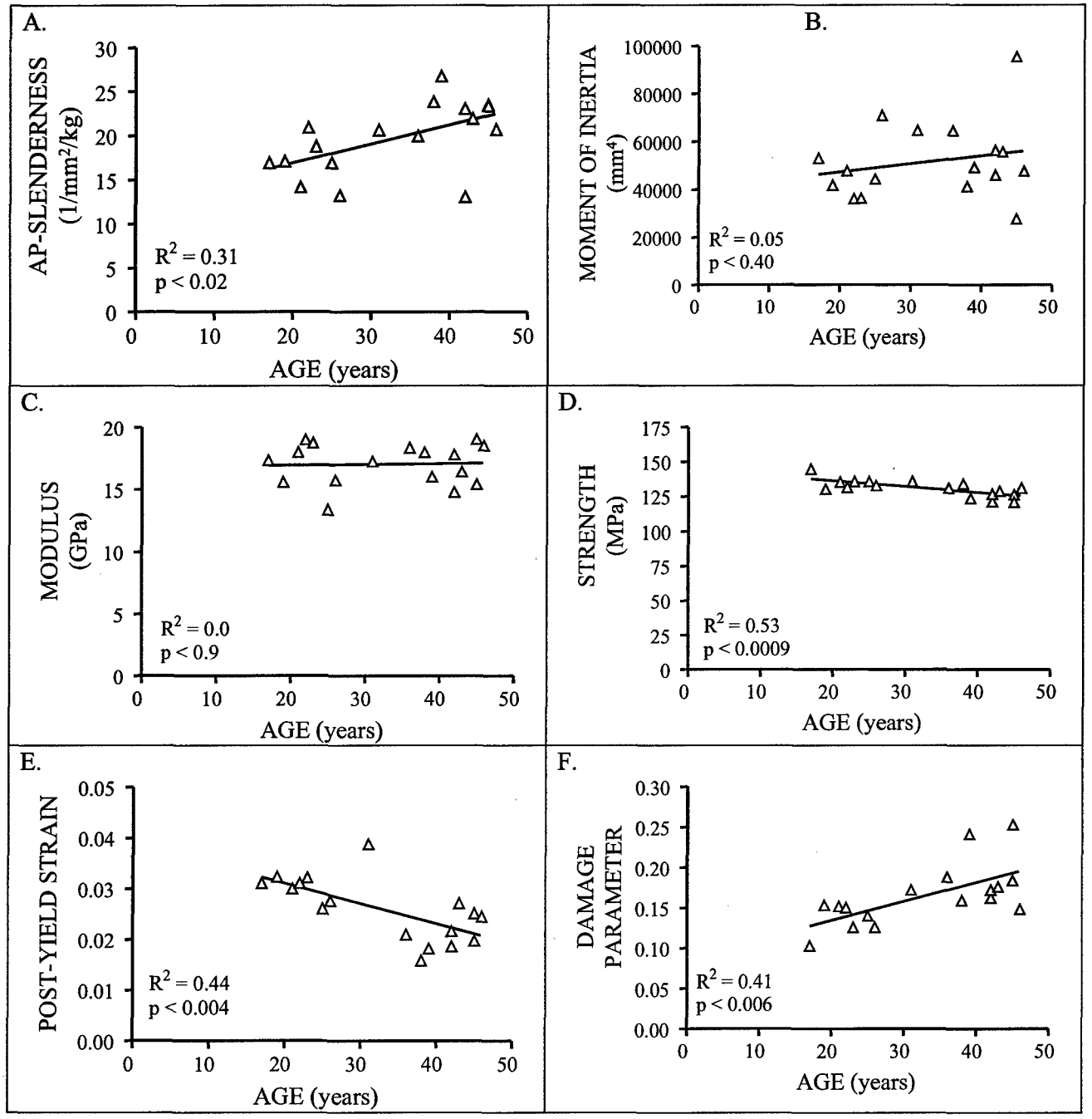
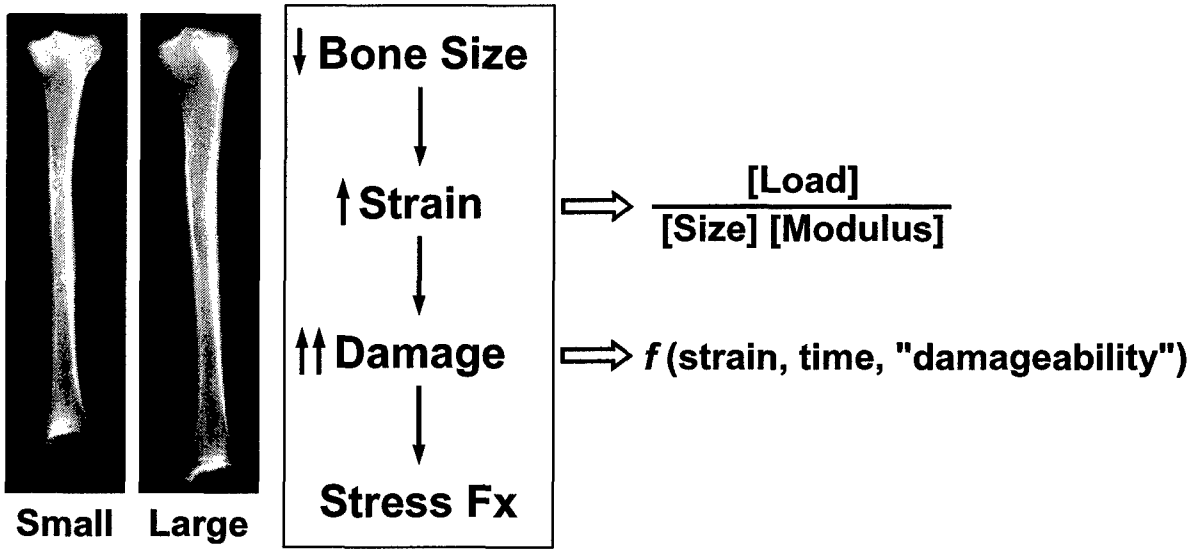


FIGURE 4. The correlation between bone size and tissue-level mechanical properties suggested that individuals with smaller bones may experience increased tissue strains (due to proportionally lower tissue modulus) and increased damage accumulation (due to increased susceptibility to accumulate damage) when subjected to vigorous loading regimens. The combination of small bones and increased damageability may contribute to the increased risk of stress fractures.



Key Research Accomplishments

The primary outcome of the grant thus far is that individuals with more slender bones appear to have different material properties. With increasing slenderness, the material is more stiff, less ductile, and more damageable. This supports are central hypothesis and may help explain why individuals with smaller tibiae are at higher risk of stress fractures.

Reportable Outcomes

Bouxien, ML, Jepsen KJ. Etiology and biomechanics of hip and vertebral fractures. *Atlas of Osteoporosis,* Second Edition. Current Medicine, Inc., Eds. Eric S. Orwoll, Stanley G. Korenman, 2003.

Jepsen K. The aging cortex: to crack or not to crack. *Osteoporos Int.* 2003 Sep;14 Suppl 5:57-66. 2003.

Tommasini SM, Nasser P, Jepsen KJ. Gender differences in bone slenderness are not related to material properties. Submitted to the Orthopaedic Research Society, July, 2002.

Tommasini SM, Morgan TG, van der Meulen MCH, Jepsen KJ. Genetic variation in vertebral mechanical properties determined by the relationship between morphological and compositional bone traits. Transactions Orthopaedic Research Society, 2003.

Jepsen KJ, Price C, Nadeau JH. Systems analysis of bone fragility. Pathways, Networks, and Systems: Theory and Experiments. Aegean Conference, 2003.

Tommasini SM, Nasser P, Jepsen KJ. The relationship between bone morphology and bone quality: Implications for stress fracture risk in young adult male tibiae. Poster and podium presentations as the American Society of Bone and Mineral Research Annual meeting, Seattle, WA, 2004.

Bird JE, Nasser P, Tommasini S, Casagrande D, Jepsen KJ. The relationship between continued periosteal apposition and bone fragility. Poster presentation at the American Society of Bone and Mineral Research Annual meeting, Seattle, WA, 2004.

Funding

The data generated by this grant provided evidence that the mouse represents an important model for understanding the genetic variability in the human skeleton. This data helped secure an RO1 grant from the NIH (AR44927) titled, "Genetic Determination of Skeletal Fragility".

Conclusions

The results to date have provided new insight into the relationship between bone morphology and tissue mechanical properties. The investigations of the mouse skeleton revealed that genetic variations in bone morphology strongly influence tissue mechanical properties through variations in matrix composition. The data suggest that a similar relationship may also exist in the human skeleton. Thus, individuals who have smaller (more narrow) tibia for their body size may compensate for the smaller geometry through variation in tissue-level mechanical properties. One of the side effects of this compensation is altered damageability which may be revealed under extreme physical activity such as that experience during military training.

References

Beck TJ, Ruff CB, Mourtada FA, Shaffer RA, Maxwell-Williams K, Kao GL, Sartoris DJ, Brodine S. Dual-energy X-ray absorptiometry derived structural geometry for stress fracture prediction in male U.S. Marine Corps recruits. *J Bone Miner Res,* 11:645-653, 1996.

Currey JD. Effects of differences in mineralization on the mechanical properties of bone. *Philos Trans R Soc Lond B Biol Sci,* 304:509-18, 1984.

Giladi M, Milgrom C, Simkin A, Stein M, Kashtan H, Margulies J, Rand N, Chisin R, Steinberg R, Aharonson Z, et al. Stress fractures and tibial bone width. A risk factor. *J Bone Jt Surg Br,* 69:326-329, 1987.

Milgrom C, Giladi M, Simkin A, Rand N, Kedem R, Kashtan H, Stein M, Gomori M. The area moment of inertia of the tibia: A risk factor for stress fractures. J Biomech 22:1243-1248, 1989.

Appendix 1

SM Tommasini, P Nasser, KJ Jepsen, The Relationship Between Bone Morphology and Bone Quality: Implications for Stress Fracture Risk in Young Adult Male Tibiae, Presented at the Annual Meeting of the American Society of Bone and Mineral Research, October, 2004.

The Relationship Between Bone Morphology and Bone Quality: Implications for Stress Fracture Risk in Young Adult Male Tibiae

SM Tommasini, P Nasser*, KJ Jepsen*
CUNY Graduate School, New York NY; *Mt Sinai School of Medicine, New York NY

Stress fractures occur among persons with normal bones, no acute injury, and are most common among elite runners and military recruits [1]. Having a narrow or slender tibia has been shown to be a major predictor of stress fracture risk and fragility [2]. Previous studies revealed that inbred mice with slender bones had increased mineral content. Although increased mineral content may have compensated for the smaller morphology by increasing tissue stiffness and strength, the increased mineral had the adverse effect of increased bone brittleness and tissue damageability under fatigue loading [3]. It is unknown whether a similar reciprocal relationship between bone geometry and bone tissue level mechanical properties also exists in the human skeleton. We assessed the biomechanical properties of tibiae from young adult males in order to determine whether whole bone geometry is a predictor of tissue fragility. Tibiae from 17 male donors (age 17-46 yrs) were measured for bone geometry [length, cortical area (CtAr), AP and ML width, moments of inertia (I_{AP}, I_{ML}, J)]. A slenderness index was defined as the inverse ratio of the section modulus to tibia length and body weight [4]: S=1/[(J/width)/(L*BW)]. The diaphyses were cut into rectangular beams and tested for monotonic properties in 4-point bending [modulus (E), strength, post-yield strain (PYε), work] and tissue damageability (*D*) in 4-point bending using the methods of Jepsen and Davy [5]. Partial correlation coefficients were determined between each geometrical parameter (CtAr, width, I_{AP}, I_{ML}, J, S) and each tissue level mechanical property (E, strength, PYε, work, *D*) while taking age into consideration. Significant correlations ($p < 0.05$) were observed between AP width and two mechanical properties related to tissue brittleness (PYε, work) indicating that the tissue of individuals with narrow tibiae was less ductile. Further, there was a significant correlation between tissue damageability and tibia slenderness ($p = 0.05$) consistent with the mouse model suggesting that slender bones may have more damageable tissue. This data indicated that not all bone is made the same way. Having a more slender tibia was associated with tissue that was less ductile and more susceptible to damage accumulation. Thus, under extreme loading conditions (e.g., military training), variation in bone quality may be a contributing factor for increased stress fracture risk in individuals with a more slender bone. [1] Milgrom et al, 1989 J Biomech 22 [2] Beck et al, 2000 Bone 27 [3] Jepsen et al, 2001 JBMR 16 [4] Selker and Carter, 1989 J Biomech 22 [5] Jepsen and Davy, 1997 J Biomech 30.

Appendix 2

SM Tommasini, P Nasser, KJ Jepsen, The Relationship Between Bone Morphology and Bone Quality: Implications for Stress Fracture Risk. Submitted to the Orthopaedic Research Society annual meeting, July, 2004.

RELATIONSHIP BETWEEN BONE MORPHOLOGY & QUALITY: IMPLICATIONS FOR STRESS FRACTURE RISK

*Tommasini, S M; **Nasser, P; **Munyoki, M; +**Jepsen, K J
*New York Center for Biomedical Engineering, City College of the City University of New York, NY, USA; +**Leni & Peter W. May Dept of Orthopaedics, Mt. Sinai School of Medicine, New York, NY, USA.
karl.jepsen@mssm.edu

Introduction: A number of risk factors for stress fracture have been identified including poor physical fitness, external hip rotation, body height, body weight, age, race, level of physical activity, motivation, prior training history, footwear, smoking, and family history of osteoporosis [1]. Currently, having a narrow tibia relative to body mass is one of the best predictors of stress fracture risk and fragility [2]. However, the reasons why individuals with more slender bones for their body size are at increased risk of stress fracture are not fully understood. Understanding the mechanisms underlying this risk factor should lead to better identification of those at risk and, ultimately, to early diagnosis, treatment, and modification of training regimens.

Based on studies of bone morphology and bone quality in genetically distinct inbred mouse strains [3], mice with slender bones had increased mineral content suggesting that bone morphology and quality might be biologically coupled to satisfy mechanical demands imposed by weight bearing. Although increased mineral content may have compensated for the smaller morphology by increasing tissue stiffness and strength, the increased mineral had the adverse effect of being associated with increased bone brittleness and poor tissue damageability under fatigue loading. The possibility that slender bones may be associated with material level variation that ultimately leads to more damageable material than larger bones has not been considered in the human skeleton. To determine whether whole bone geometry is a predictor of tissue fragility we conducted a biomechanical and compositional evaluation of the tibiae from young adult males.

Methods: Tibiae from 17 male donors (age 17-46 yrs) with no known orthopaedic pathologic conditions were obtained and measures of bone morphology including cortical area (CtAr), AP and ML width, moments of inertia (I_{AP}, I_{ML}), and polar moment of inertia ($J = I_{AP}+I_{ML}$) were determined from mid-diaphyseal cross-sections at 30, 50, and 70% of the total tibia length. A slenderness index (S) was defined as the inverse ratio of the section modulus (J/width) to tibia length and body weight:

$$S = 1/[(J/(\text{width}))/(L*BW)], \quad (1)$$

where L = tibia length (cm) and BW = body weight (kg).

A total of 8 cortical bone samples (2.5mm x 5mm x 55mm) were machined from the diaphysis of each bone and split into 2 tests groups. First, monotonic failure properties were assessed by loading to failure in 4-point bending. Load and deflection were converted to stress and strain using equations which take yielding into consideration [4]. Mechanical properties measured were modulus (E), strength, work, and post-yield strain (PYε) as a measure of brittleness. Second, tissue damageability was assessed using a fifteen-cycle damage accumulation protocol in 4-point bending similar to that described previously [5]. The overall damage was the sum of each damage cycle plus interaction between existing damage and the increased applied load. The overall damage accumulation (D) was calculated by comparing the stiffness of the first and last diagnostic tests such that:

$$D = 1 - S_{15}/S_0, \quad (2)$$

where S_{15} is the stiffness of the last diagnostic cycle and S_0 is the average stiffness of the first two diagnostic cycles and the first damage cycle.

The density, ash content, and water content were determined for each sample retrieved from the monotonic tests. Specimen volume, submerged weight, hydrated weight, dry weight, and ash weights were determined using Archimedes' principal as described previously [6].

To determine whether bone morphology was related to tissue level material properties, partial correlation coefficients were determined between each morphological and compositional parameter (CtAr, width, I_{AP}, I_{ML}, J, S, ash content) and each tissue level mechanical property (E, strength, PYε, work, D) while taking age into consideration.

Results: Significant correlations ($p < 0.05$) were only observed between post-yield properties and bone size and morphology (Table 1). AP width correlated with PYε and work indicating that the tissue of individuals with narrow tibiae was less ductile (Fig. 1). Further, there was a significant correlation between tissue damageability and tibia slenderness ($p = 0.05$) consistent with the mouse model suggesting that slender bones accumulate more cracks under equivalent loading conditions (Fig. 2). The relationship between mechanical properties and morphology could not be explained by differences in composition, as age corrected ash content did not correlate with any mechanical or geometric parameter (Table 1).

Discussion: This data indicated that not all bone is made the same way. Post-yield material properties related to damageability and fragility were also related to bone morphology. Having a more slender tibia was associated with tissue that was less ductile and more susceptible to damage accumulation. However, unlike the mouse model, increased mineral content was not associated with whole bone morphology and therefore not a strong explanatory variable of the variation in tissue fragility. Physical conditioning, which along with having a narrow tibia is a risk factor for stress fracture [7], is related to bone remodeling and ultimately affects microstructure. It has been reported that stiff and strong skeletons are not only developed by mineralizing collagen, but also by orienting the spatial disposition of the microstructural elements within the mineralized material [8]. Thus, under extreme loading conditions (e.g., military training), variation in bone quality, specifically microstructure, may be a contributing factor for increased stress fracture risk in individuals with a more slender bone.

Table 1. Pearson correlation coefficients are shown with p-values in parentheses. Data corrected for age based on linear regression method. Significant correlations in **bold**.

	E	Strength	Work	PYε	*D*	Ash Content
CtAr	-0.24	0.03	0.40	-0.23	-0.07	
	(0.35)	(0.90)	(0.14)	(0.11)	(0.38)	(0.79)
AP	-0.09	-0.03	**0.57**	**0.70**	-0.16	-0.17
Width	(0.74)	(0.90)	**(0.02)**	**(0.01)**	(0.55)	(0.52)
ML	-0.32	-0.22	0.34	0.41	-0.19	-0.23
Width	(0.21)	(0.39)	(0.18)	(0.11)	(0.46)	(0.37)
I_{AP}	-0.45	-0.10	0.25	0.32	-0.27	-0.13
	(0.07)	(0.70)	(0.34)	(0.21)	(0.30)	(0.63)
I_{ML}	-0.39	-0.18	0.22	0.28	-0.25	-0.21
	(0.12)	(0.50)	(0.39)	(0.28)	(0.33)	(0.42)
J	-0.43	-0.13	0.24	0.31	-0.27	-0.16
	(0.08)	(0.61)	(0.35)	(0.23)	(0.30)	(0.54)
AP S	0.36	0.10	0.09	0.03	**0.47**	0.13
	(0.15)	(0.69)	(0.72)	(0.92)	**(0.05)**	(0.62)
ML S	0.23	-0.01	0.04	-0.05	0.42	0.01
	(0.39)	(0.96)	(0.89)	(0.84)	(0.09)	(0.80)
Ash	0.31	0.11	0.27	0.19	0.13	
Content	(0.23)	(0.67)	(0.29)	(0.46)	(0.62)	

Fig. 1. Correlation between AP width and post-yield properties.

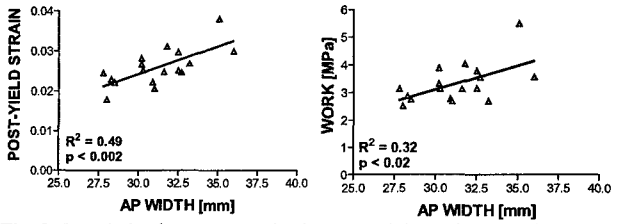
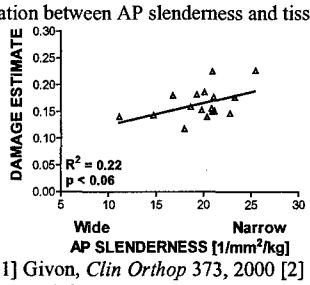


Fig. 2. Correlation between AP slenderness and tissue damageability.



References: [1] Givon, *Clin Orthop* 373, 2000 [2] Beck, *Bone* 27, 2000 [3] Jepsen, *JBMR* 16, 2001 [4] Tommasini, *Trans 50th ORS* 29, 2004 [5] Jepsen, *J Biomech* 30, 1997 [6] Jepsen, *J Orthop Res* 14, 1996 [7] Beck, *JBMR* 11, 1996 [8] Ferretti, *Mech Ageing Dev* 124, 2003.

Acknowledgements: DOD (DAMD17-01-1-0806).